



Influence of Metabolic Syndrome on the Recovery from Idiopathic Sudden Sensorineural Hearing Loss

Miguel Sá Breda¹ Ana Sousa Menezes¹ Tiago Gil Oliveira^{2,3,4} Luís Dias¹

¹Otorhinolaryngology and Head & Neck Surgery Department, Hospital de Braga, Braga, Portugal

²Neuroradiology Department, Hospital de Braga, Braga, Portugal

³Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

⁴ICVS/3B's, Portuguese Government Associate Laboratory, Braga/Guimarães, Portugal

Address for correspondence Miguel Sá Breda, MSc/MD, Otorhinolaryngology and Head & Neck Surgery Department – Hospital de Braga, Sete Fontes – São Victor 4710-243 Braga, Portugal (e-mail: miguelbreda@gmail.com).

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Abstract

Introduction Idiopathic sudden sensorineural hearing loss (ISSHL) is a disabling otologic urgency whose etiopathogenesis is still controversial. Only in recent years metabolic syndrome (MetS) has been implicated as a possible aggravating factor in the prognosis of recovery from ISSHL.

Objective To assess whether the preexistence of MetS interferes on hearing recovery levels.

Methods Retrospective cohort study composed of adult (> 18 years old) ISSHL patients admitted for treatment between January 2015 and December 2019. To diagnose ISSHL, we used pure-tone audiometry, and identified MetS patients based on the criteria of the United States National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III). The treatment protocol comprised hospitalization for five days for the intravenous administration of dexamethasone, audiometric surveillance, imaging and blood analyses, and, based on recovery, the planning of rescue treatments (intratympanic administration of dexamethasone and/or hyperbaric oxygen). The Siegel criteria were used to evaluate the hearing outcomes.

Results The final sample was composed of 81 patients, 48 without MetS (nMetS) and 33 with MetS. Regarding the Siegel recovery category, the nMetS group had significantly better results ($p = 0.001$), with 44% of complete recoveries against 6% in the MetS, and 58% of the MetS patients had the worst outcome, contrasting with 27% in the nMetS group. The nMetS group had an overall better evolution in terms of hearing recovery and had a significant improvement in the median hearing gain (20.6 dB versus 8.8 dB; $p = 0.008$). Additionally, the multivariate analysis revealed that the presence of MetS is a significant risk factor for a worse outcome (odds ratio [OR] = 0.30; 95% confidence interval [95%CI] = 0.10–0.85).

Conclusion Regardless of age, gender, the initial audiometry threshold, and autoimmunity, MetS is a clear risk factor for a worse outcome regarding the recovery of hearing after ISSHL.

Keywords

- ▶ hearing loss
- ▶ idiopathic sudden sensorineural hearing loss
- ▶ metabolic syndrome
- ▶ hearing recovery

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as an otologic urgency with a rapid onset of hearing loss, of at least 30 dB (dB) in 3 or more consecutive frequencies over 72 hours, disturbing 1 or both ears.¹ The incidence varies between 5 to 30 cases per 100 thousand patients/year.^{1,2} The vast majority of cases (90%) are idiopathic, without a known etiology, despite adequate investigation.¹⁻³ Classically, the most debated causes for this pathology are viral infection^{2,4} and vascular disorders,² such as circulatory disturbance in the area of the anterior inferior cerebellar artery related to special cochlear vulnerability, vestibular schwannoma, and perilymphatic fistula.¹⁻³ Only in the last few years, the link between cardiovascular factors and ISSHL started to be evaluated, and disorders such as diabetes mellitus (DM), arterial hypertension (AHT), hyperlipidemia (HYL), ischemic heart disease, and obesity have been shown to play an important role.^{1,2,5} On the other hand, ISSHL was regarded as a possible sign preceding the development of ischemic stroke.⁵⁻⁷ Despite this evidence, it is still controversial if the occurrence of ISSHL and its recovery should be considered cardiovascular risk biomarkers. The knowledge of this association would be important for the treatment of ISSHL and to address these cardiovascular preconditions in ISSHL patients.

In the last decades, a trend towards a change in the metabolic patterns of society has been well recognized, with metabolic syndrome (MetS) being an increasingly common condition.⁸⁻¹⁰ In 2015, the reported prevalence in Europe was of 24%,⁸ with a higher prevalence among women and with an age-associated prevalence increase in all published cohorts.⁸⁻¹⁰ Even more concerning is that this trend is also observed in younger populations, who present higher obesity rates that necessarily increase the odds of developing MetS.^{8,9} Moreover, MetS is a risk factor for stroke, cardiac infarction, and cardiovascular-related mortality.⁸⁻¹⁰ Despite these associations, there are limited studies addressing the impact of MetS on the level of recovery from ISSHL. Therefore, the present work aims to clarify whether MetS affects the posttreatment outcomes of ISSHL.

Material and Methods

We designed a retrospective cohort study composed of ISSHL patients admitted for treatment to a tertiary university hospital from January 2015 to December 2019. The hospital's ethics committee approved the study, which was conducted from July to November 2020.

Included Patients and ISSHL Treatment Protocol

Initially, 104 consecutive patient records were analyzed, and, after applying the inclusion/exclusion criteria, a final sample of 81 ISSHL patients were obtained. All of the patients visited our Otorhinolaryngology Urgency Department and presenting unilateral ISSHL that developed within 72 hours, with, at least, reduction of 30 dB at 3 or more consecutive frequencies. Upon admission, all patients were diagnosed through

pure-tone audiometry (at least with assessments of the frequencies of 0.5 kHz, 1 kHz, 2 kHz and 4 kHz) and tympanometry to exclude other middle-ear conditions. Moreover, we performed: a routine ear, nose, and throat (ENT) examination; collection of a blood sample for the analysis of the hemogram of the hepatic and renal functions; a lipidic panel, including total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) lipoprotein cholesterol, as well as triglycerides (TG); glucose screening with C-reactive protein; an autoimmunity panel (for antinuclear antibodies [ANA], antineutrophil cytoplasmic antibodies [ANCA], and antibodies to the inner ear antigen [anti-68kD]); and an infectious panel (for syphilis, lyme disease, herpes I and zoster, Epstein-Barr virus, toxoplasmosis, and rubella). It is within our protocol to propose to patients their hospitalization for complete intravenous (IV) treatment for five days, to undergo magnetic resonance scan to exclude stroke and vestibular schwannoma or other cerebellopontine angle conditions, and, finally, to undergo audiometric evaluations on the third and fifth (last) days of the IV treatment to monitor their recovery progress. The daily treatment includes the IV administration of 5 mg of dexamethasone twice a day, the oral administrations of 5 mg of diazepam and 40 mg of pantoprazole, and insulin when serum glucose is \geq 160 mg/dL. The following rescue treatments were offered to all patients, after informed consent, at the third or last days of hospitalization, in case of absence of audiometric recovery or of recovery below 50%: 1) intratympanic (ITY) dexamethasone (4 mg/mL) injection on a weekly basis (maximum of 3 injections), completed after patient discharge; and 2) hyperbaric oxygen (HBO), planned on the fifth/last day of the IV treatment. In regular conditions, HBO was started during the second week of treatment, and it was administered for 20 sessions in an HBO center located 60 km from our medical center. It was possible to simultaneously propose HBO and ITY dexamethasone. After hospital discharge, all patients were prescribed a slow tapering of corticosteroid with prednisolone for 15 days. They were followed up weekly on the first month for audiometric surveillance and, if necessary, repeated ITY dexamethasone. After that, we requested a monthly visit until the sixth month, and the following visits were under appointment or patient request, with at least one yearly visit.

The exclusion criteria were age under 18 years, history of head or acoustic trauma, Ménière disease, exposure to ototoxic agents (such as aminoglycosides), more than three days of delay following the onset of symptoms to start the treatment protocol, ipsilateral otologic history (surgical or non-surgical), diagnosis of stroke or vestibular schwannoma after imaging, evidence of infectious disease, and patient refusal to enroll in the protocol. From an initial sample of 104 patients, 10 were excluded due to viral infection (all of the cases caused by varicella zoster, diagnosed after blood sample analysis according to the protocol), 4, due to anterior inferior cerebellar artery (AICA)/cerebellum stroke, 4, due to posthead trauma hearing loss, 3, due to vestibular schwannoma, 1, due to age $>$ 18 years, and 1, due to refusal to enroll in the protocol.

Table 1 Siegel¹¹ criteria of hearing improvement

Type of recovery	Hearing recovery
I – Complete	Patients whose final hearing level (pure-tone average) is better than 25 dB regardless of the amount of the gain
II – Partial	Patients who show > 15 dB of gain and whose final hearing level (pure-tone average) is between 25 dB and 45 dB
III – Slight	Patients who show > 15 dB of gain and whose final hearing level (pure-tone average) is poorer than 45 dB
IV – No improvement	Patients who show < 15 dB of gain

Note: The higher the level, the worse the outcome.

Audiometric Assessment and Hearing Recovery Criteria

All patients underwent pure-tone average (PTA) audiometry and acoustic immittance (tympanometry) evaluations according to the standards of the American Academy of Audiology. The PTA threshold was obtained from the calculated mean of four frequencies (0.5 kHz, 1 kHz, 2 kHz, and 4 kHz). The PTA threshold recognition was set at 120 dB HL. The normal hearing threshold, following international standards, was considered to be 20 dB HL. To classify hearing recovery, our primary outcome, we used the Siegel¹¹ criteria (►Table 1). The audiometric assessment was performed upon admission, and on the third and last IV administration and hospitalization days, prior to any ITY dexamethasone injections, during HBO, and, to all patients, in the sixth months of follow-up.

Assessment of Medical History and MetS Definition

When hospitalized, all patients had their medical history taken, including DM, AHT, HYL, concomitant active medications for these conditions, and smoking habits. The anthropometric parameters of weight, height and body mass index (BMI) were assessed by a nursing team on day one.

The criteria used to diagnose MetS were those of the United States National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),¹² with one adapted criterion for abdominal obesity, because waist circumference was not routinely assessed. Therefore, MetS was considered the presence of 3 or more of the following elements: 1) blood pressure > 130/85 mmHg or drug treatment for elevated blood pressure; 2) fasting TG level > 150 mg/dL, or drug treatment for hypertriglyceridemia; 3) HDL level < 40 mg/dL in males, and < 50 mg/dL in females; 4) fasting plasma glucose level \geq 100 mg/dL, or drug treatment for hyperglycemia, for patients who had DM; 5) adapted criteria for abdominal obesity, with BMI > 25 Kg/m² in both males and females. After this methodological approach, we divided the 81 patients into 2 groups: 48 without MetS (nMetS), and 33 with MetS.

Statistical Analyses

All statistical analyses were performed using the STATA (StataCorp LLC, College Station, TX, US) software, version 14.1. The continuous variables are presented as means and standard deviations or medians and interquartile ranges, after the distribution analysis, and the categorical and ordinal variables, as frequencies and percentages. Associations between groups were tested for categorical variables with the Chi-squared and Fisher exact tests. To compare the continuous variables, we used the independent *t*-test, or, in case of continuous non-normally distributed or ordinal variables, the Wilcoxon rank-sum test. A multivariate analysis was performed to assess the predictors of our primary outcome – hearing recovery according to the Siegel¹¹ criteria – using binary logistic and ordinal regression models to estimate its odds ratio (OR) and 95% confidence interval (95%CI). Interactions between MetS and other variables were tested, namely age, gender, and initial PTA. Statistical significance was set at $p < 0.05$.

Results

Demographic Characterization of the Study Groups

Overall, we included 81 patients. The nMetS group was composed of 48 patients, and the MetS group, of 33 patients. ►Table 2 summarizes all the relevant demographic and clinical aspects of our sample. Both groups were similar concerning gender distribution, the affected ear, accompanying symptoms, smoking habits, and autoimmune profile. On the other hand, nMetS patients were significantly younger than MetS patients (mean age of 46 years versus 60 years respectively; $p < 0.05$).

The most common hearing loss pattern on the audiogram was both pantonal loss without total hearing loss, and total hearing loss. The MetS patients required rescue treatment with ITY dexamethasone more often than the nMetS group (76% versus 48% respectively; $p = 0.016$), and, in the vast majority of the cases, 3 injections were administered. Both groups recurred to HBO, with a slight preponderance of the MetS group (12% versus 8%; $p > 0.05$).

As expected, the metabolic and cardiovascular profiles of the MetS group were significantly worse, with a higher prevalence of AHT, HYL, DM (the latter only present in the MetS group). Additionally, the mean BMI was of 29 Kg/m² (borderline class-I obesity), and 79% had the diagnosis of MetS based on the presence of at least 3 of the aforementioned criteria for it. The TG and HDL serum values were globally worse in MetS patients. Moreover, the MetS group had more female patients with a higher mean age (60 years old), which is in line with a 2017 report by Moore et al.⁹

Hearing Recovery Outcomes

As depicted in ►Fig. 1, we found that the nMetS group had an overall better evolution and a significant improvement in hearing gain compared to the MetS group (20.6 dB versus 8.8 dB respectively; $p = 0.008$). However, the nMetS group

Table 2 Demographic and clinical characteristics of the study sample

		nMetS (n = 48)		MetS (n = 33)		p-value	
Gender – n (%)	Female	28 (58.3%)		17 (51.5%)		0.54	
Age (years)	Mean ± standard deviation	46 ± 15		60 ± 10		< 0.001*	
Affected ear – n (%)	Right ear	23 (47.9%)		11 (33.3%)		0.19	
Accompanying symptoms – n (%)	Tinnitus	37 (77.1%)		21 (63.6%)		0.18	
	Vertigo	15 (31.3%)		12 (36.4%)		0.63	
Initial pure-tone average (dB)	Median (interquartile range)	63 (40–103)		78 (60–114)		0.029*	
Audiogram loss pattern – n (%)	Pantonal without cophosis	13 (27.1%)		16 (48.4%)		0.053	
	Cophosis	15 (31.3%)		11 (33.3%)			
	Low frequencies	14 (29.2%)		2 (6.1%)			
	High frequencies	4 (8.3%)		2 (6.1%)			
	Preserved intermedium frequencies	1 (2.1%)		2 (6.1%)			
	Lost intermedium frequencies	1 (2.1%)		0			
Rescue treatment – n (%)	Intratympanic dexamethasone	23 (47.9%)		25 (75.8%)		0.016*	
	Number of intratympanic dexamethasone: median (interquartile range)	3 (2–3)		3 (2–3)		0.78	
	Hyperbaric oxygen	4 (8.3%)		4 (12.1%)		0.71	
Smoking habits – n (%)	Active	9 (18.8%)		6 (18.2%)		0.91	
Body Mass Index (Kg/m ²)	Mean ± standard deviation	24.8 ± 3.8		28.8 ± 3.5		< 0.001*	
Arterial hypertension – n (%)	Known/Active medication	12 (25.0%)		23 (69.7%)		< 0.001*	
Hyperlipidemia – n (%)	Known/Active medication	19 (39.6%)		31 (93.9%)		< 0.001*	
HDL (mg/dL)	Median (interquartile range)	Male 58 (42–80)	Female 72 (55–78)	Male 46 (35–58)	Female 56 (50–66)	Male patients: 0.038*	Female patients: 0.08
High-density lipoprotein cholesterol (mg/dL) – global	Median (interquartile range)	60 (50–79)		52 (43–64)		0.008*	
Tryglicerides (mg/dL)	Median (interquartile range)	92 (60–120)		111 (106–175)		< 0.001*	
Diabetes mellitus – n (%)	Known/Active medication	0		12 (36.4%)		< 0.001*	
Fasting glucose blood level (mg/dL)	Median (interquartile range)	94 (85–101)		111 (100–136)		< 0.001*	
MetS components – n (%)	0	19 (39.6%)					
	1	19 (39.6%)					
	2	10 (20.8%)					
	3			26 (78.8%)			
	4			5 (15.2%)			
	5			2 (6.1%)			
Serum autoantibodies – n (%)	Overall	8 (16.7%)		8 (24.2%)		0.55	
	ANA	7 (14.6%)		7 (21.2%)		0.58	
	ANCA	1 (2.1%)		1 (3%)		0.69	
	Anti-68 kD	0		0			

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-68 kD, antibodies to the inner ear antigen; MetS, with metabolic syndrome; nMetS, without metabolic syndrome.

Note: In the nMets and MetS column, the numbers in bold represents the central tendency or equivalent. In the last column the numbers in bold are highlighted when there is any statical significance.

had a significantly better initial PTA than the MetS group (62.5 dB versus 77.5 dB respectively; $p = 0.029$), and, at the end of the follow-up, the nMetS group had a significantly better median PTA threshold than the MetS group (30.6 dB versus 62.5 dB respectively; $p = 0.001$). On the other hand, the recovery evolution in the MetS group was less pronounced and with a lower dB increment. It should be highlighted that despite the fact that the nMetS group had a better initial PTA, the final gain was significantly higher in

the nMetS group, and even higher than the initial difference between the two groups, which demonstrates that the results obtained do not just depend on the better starting point of nMetS patients.

Regarding the analysis of the primary outcome – hearing recovery according to the Siegel¹¹ criteria – (► Fig. 2, ► Table 3) the nMetS group obtained better results ($p = 0.001$), with complete recovery (Siegel I) in almost 50% of the patients.

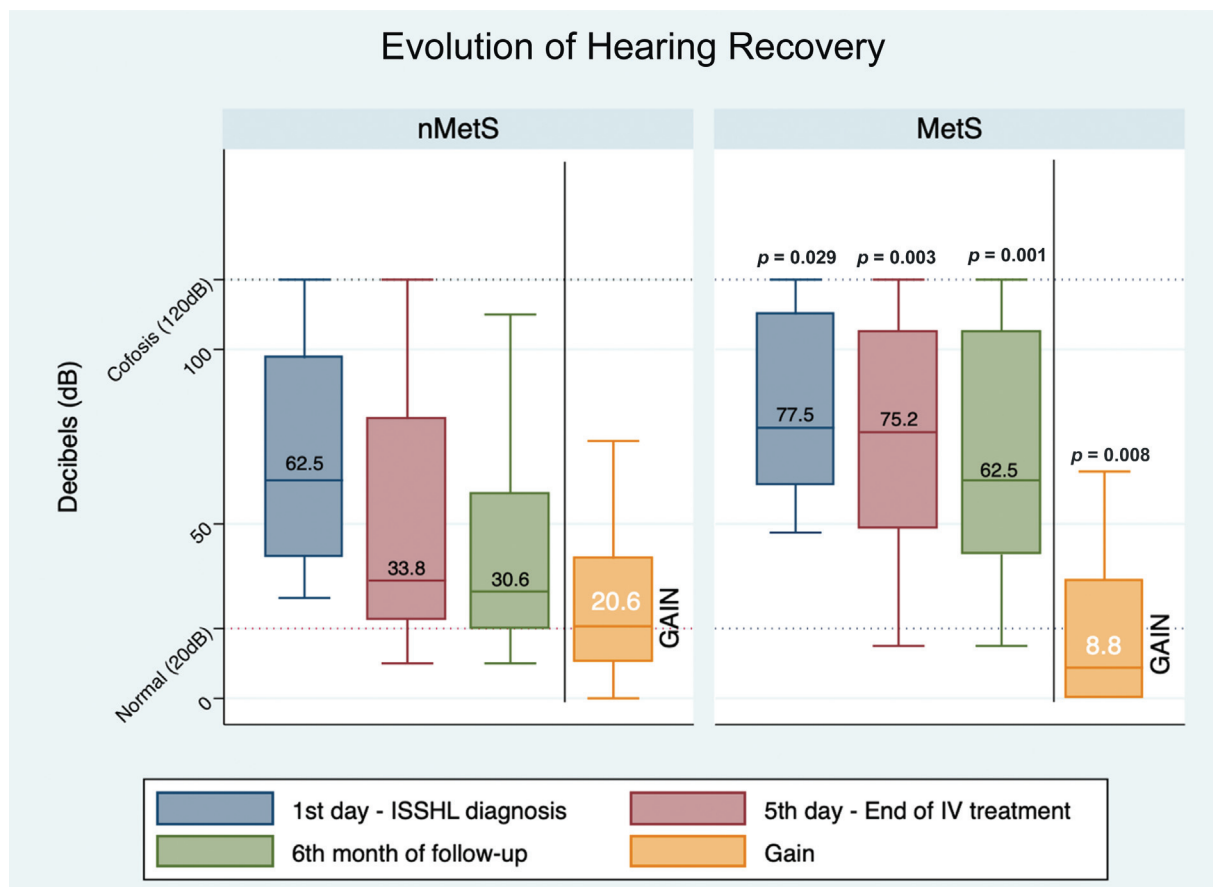


Fig. 1 Evolution of Hearing Recovery among the study sample. The lower, the better, except for the gain. Comparison of the median PTA between the nMetS and MetS groups and overall median dB gain. Abbreviations: ISSHL, idiopathic sudden sensorineural hearing loss; IV, intravenous; MetS – with metabolic syndrome; nMetS – without metabolic syndrome.

The MetS group presented worse outcomes. In fact, when an improvement occurred, it was rarely complete, and the majority of these patients (73%) did not recover (Siegel IV) or had a slight recovery (Siegel III).

Overall, our results showed a clear trend linking MetS to worse outcomes.

Establishing Predictors – Multivariate Analysis

We intended to establish predictors for our hearing recovery outcome, focusing on our binary *recovery* variable (explained in ▶ Table 4, ▶ Fig. 3) and the *Siegel recovery* ordinal variable, controlling for potential confounders such as age, gender, and autoimmunity. Every additional 20 dB in the PTA threshold at diagnosis was revealed to be a predictor of a worse Siegel score in all analyzed models (**any level of recovery** – OR = 0.64; 95%CI: 0.45–0.93; **partial hearing recovery** – OR = 0.42; 95%CI: 0.26–0.67; **complete hearing recovery** – OR = 0.49; 95%CI: 0.29–0.83; and **Siegel outcome** – OR = 0.54; 95%CI: 0.39–0.76).

Concerning the impact of MetS on the prognosis of recovery from ISSHL, only the 4.4 regression model (▶ Table 4) showed evidence that it was a risk factor for a worse hearing outcome (OR = 0.30; 95%CI: 0.10–0.85), controlling for age, gender, initial PTA, and autoimmunity. So, in this model, a MetS patient has a 70% decrease in the odds of a better outcome. Of all the tested regression models, we

emphasize the “4.4,” (▶ Table 4) since it is more comprehensive, inclusive, and covers all possible hearing recovery outcomes. The test of the interaction among variables, namely MetS and age, gender and initial PTA, did not reveal significant results (all *p*-values > 0.20). Therefore, having MetS and a higher initial PTA threshold are predictors of a worse outcome. We also noted a trend, although not significant, towards better outcomes among women.

Discussion

The interest in the relationship between MetS and ISSHL is recent, and only in 2015¹³ it was first reported. Although the diagnosis of ISSHL as an audiometric entity does not generate discussion, the true causes underlying ISSHL are still unknown.^{1,2} This awareness arose when it was noticed that not all patients developed a similar pattern of symptoms, and, in this cohort, regardless of MetS concomitancy, more than 60% of patients end up having tinnitus, which itself may be the manifestation of hypoacusis.¹⁴ Even when analyzing the initial ISSHL audiometric curve, the authors¹⁴ did not identify a typical one. So, even though it is clear when patients have sudden hearing loss, it is still intriguing if they all really have the same underlying condition. For many years, it was believed that the etiology of ISSHL would be closely linked to viral and even vascular causes.^{1,2,14}

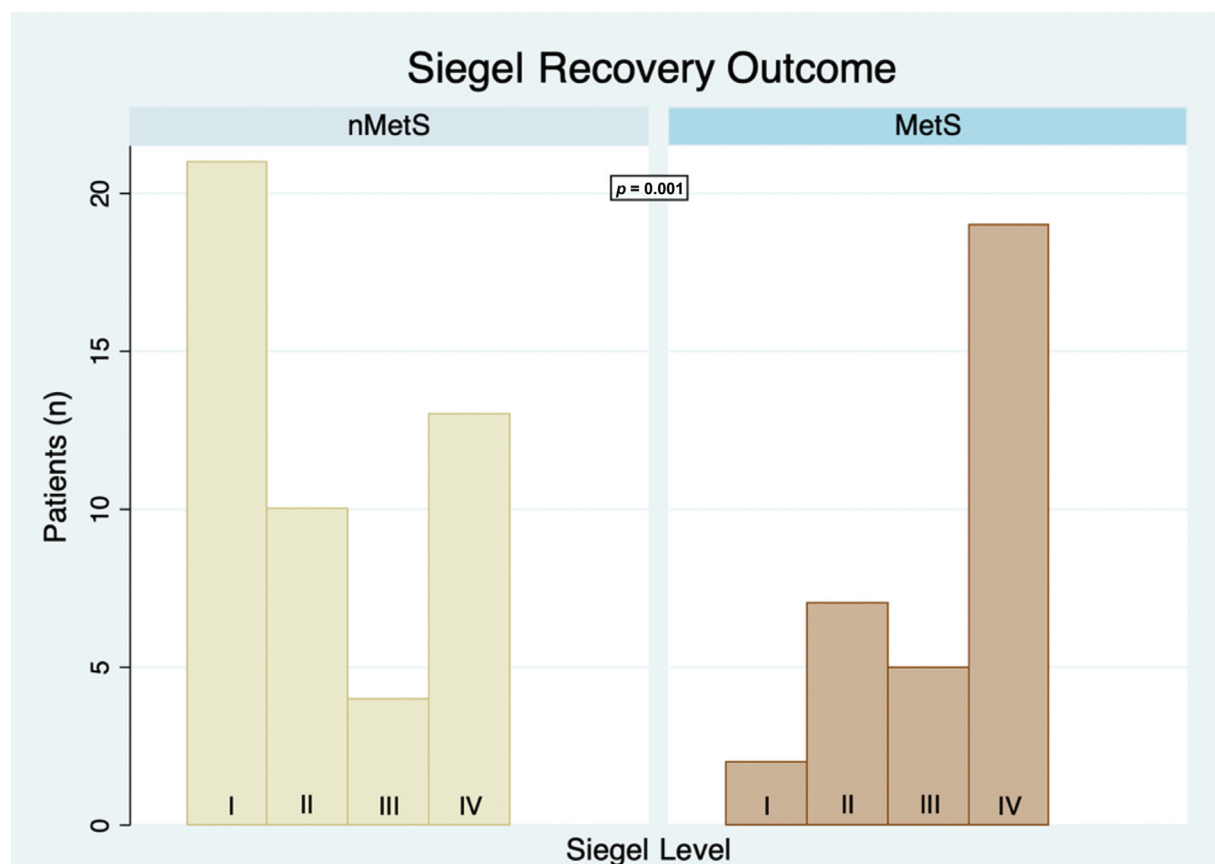


Fig. 2 Siegel Recovery Outcome. The higher the level, the worse the outcome. The nMetS group had significantly better outcomes ($p = 0.001$). Abbreviations: MetS – with metabolic syndrome; nMetS – without metabolic syndrome.

Table 3 Hearing recovery outcomes after 6 months of follow-up

	nMetS (n = 48)	MetS (n = 33)	p-value
RECOVERY Siegel I and II – n (%)	31 (64.6%)	9 (27.3%)	0.001*
NO RECOVERY Siegel III and IV – n (%)	17 (35.4%)	24 (72.7%)	
Siegel I – n (%)	21 (43.8%)	2 (6.1%)	0.001*
Siegel II – n (%)	10 (20.8%)	7 (21.2%)	
Siegel III – n (%)	4 (8.3%)	5 (15.2%)	
Siegel IV – n (%)	13 (27.1%)	19 (57.6%)	
Subjective improvement (reported by the patient) – n (%)	36 (75%)	15 (45.5%)	0.007*

Abbreviations: MetS, with metabolic syndrome; nMetS, without metabolic syndrome.

Therefore, there is still a long path to identify the etiopathogenesis of sudden hearing loss, at least in the cases referred to as idiopathic. In the present study, the cases were identified as idiopathic taking into account our exhaustive protocol, which excludes classic viral/infectious, vascular, autoimmune, and oncological causes. Accordingly, other studies^{2,5–7,13,15} were published, which attempted to correlate ISSHL with other potential risk factors such as

cardiovascular, metabolic, or autoimmune conditions. One of the factors that will definitely help to explain the pathophysiological mechanism, and even refine the diagnosis of sudden hearing loss, is the improvement in imaging exams, namely high-field magnetic resonance imaging of the inner ear.^{16,17}

In the present article, our hypothesis focused on the possible relationship between the prevalence of MetS and worse hearing recovery outcomes after ISSHL, since MetS has an increasing incidence worldwide,⁹ in Europe,⁸ and particularly in Portugal¹⁰ (with prevalence rates very close to those of the the United States: ~ 23%). Supporting our hypothesis, Zhang et al.,¹⁵ in 2019, published a study with a robust sample size, and concluded that MetS had a negative effect on hearing recovery. However, this study was based on an Asian population with characteristics different from those of the sample of the present study, particularly younger patients (42 to 44 years old), and the multivariate analysis was performed only from the point of view of *recovery* as a binary outcome. In the present study, we decided to complete this analysis considering all stages of the Siegel outcomes. We reinforce this, since a binary-outcome analysis of *recovery* (Siegel I, II) versus *no recovery* (Siegel III, IV) would lose the discriminatory power of the best recovery cases (Siegel I). This is precisely what was observed in the present study: *recovery* – nMets: 65%; MetS: 27% versus *Siegel I* – nMets: 44%; MetS: 6% (► **Table 3**, ► **Fig. 2**), with clear overestimation of the success of the MetS group in

Table 4 Results of the multivariate analysis

Regression model and outcome		Predictors	Odds ratio	95% confidence interval	p-value
4.1 Any level of hearing recovery	<i>Binary logistic regression</i> Outcome: 1. Any recovery (Siegel I, II, III) versus 0. No recovery at all (Siegel IV)	With metabolic syndrome	0.38	0.12–1.24	0.10
		Per 20 dB of increment in initial pure-tone average	0.64	0.45–0.93	0.018*
		Female	2.46	0.88–6.92	0.09
		Per 10 years of increment in age	0.97	0.65–1.44	0.87
		Serum autoantibodies	0.85	0.25–2.86	0.79
4.2 At least partial hearing recovery	<i>Binary logistic regression</i> Outcome: 1. Recovery (Siegel I, II) versus 0. No recovery (Siegel III, IV)	With metabolic syndrome	0.33	0.09–1.23	0.10
		Per 20 dB of increment in initial pure-tone average	0.42	0.26–0.67	< 0.001*
		Female	3.16	0.97–10.26	0.06
		Per 10 years of increment in age	0.87	0.56–1.36	0.54
		Serum autoantibodies	1.13	0.31–4.15	0.86
4.3 Complete hearing recovery	<i>Binary logistic regression</i> Outcome: 1. Complete recovery (Siegel I) versus 0. Without complete recovery (Siegel II, III, IV)	With metabolic syndrome	0.22	0.04–1.32	0.10
		Per 20 dB of increment in initial pure-tone average	0.49	0.29–0.83	0.008*
		Female	1.94	0.54–7.04	0.31
		Per 10 years of increment in age	0.64	0.38–1.08	0.10
		Serum autoantibodies	1.54	0.34–7.07	0.97
4.4 Better Siegel outcome	<i>Ordinal logistic regression</i> Outcome: Ordinal Siegel hearing recovery level	With metabolic syndrome	0.30	0.10–0.85	0.023*
		Per 20 dB of increment in initial pure-tone average	0.54	0.39–0.76	< 0.001*
		Female	2.40	0.96–5.99	0.06
		Per 10 years of increment in age	0.86	0.62–1.21	0.40
		Serum autoantibodies	1.02	0.34–3.08	0.97

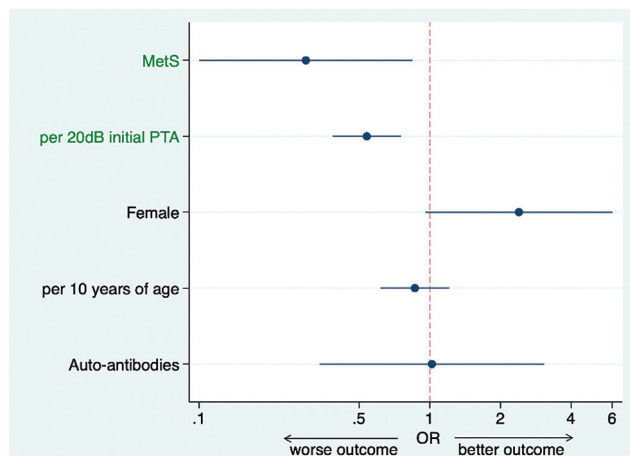


Fig. 3 Better Siegel outcome 4.4 regression model – odds ratio plots.

the first binary-outcome analysis. Additionally, Zhang et al.¹⁵ did not mention neither controlled for autoimmunity.

The mechanism underlying worse outcomes among MetS patients is still speculative. For instance, insulin resistance and the consequent hyperglycemia, as well as hyperlipidemia and prothrombotic/proinflammatory states,¹² which are characteristics of MetS, can lead to endothelial changes in small vessels that can be harmful to the cochlea and the microcirculatory vessels of the Corti organ,^{12,13,15} potentially leading to worse outcomes. Diabetes mellitus is consistently associated with a worse recovery after ISSHL,⁵ and, even in the sample of the present study, 8 out of the 12 DM patients presented no recovery, and 6 of these, Siegel IV. In summary, in addition to observing that the sum of each MetS diagnostic criteria was negatively associated with worse outcomes in terms of hearing recovery, we conclude,

based on our sample, that these patients will require more rescue treatments, despite the burden of their own morbidity.^{13,15,18} Thus, the rescue treatments (ITY dexamethasone and HBO) offered since the beginning of the treatment might be a potential intervention of choice in these patients.

As we would expect, the initial PTA threshold appears crucial for the success of the recovery, as demonstrated in other studies.^{2,13,15} This is likely due to the size of injured cochlear area (hair cells), which would be linked to a worsening of the initial PTA.¹⁹

The main limitations of the present work were the retrospective methodology and the fact that the exact time of exposure to MetS was not properly recorded or corrected for each patient. Even though the BMI calculation was an alternative and valid metric for the waist circumference to consider as a MetS diagnostic criterion, we believe it was a fair approach. Finally, we acknowledge that the fact that the HBO center was not located within our facilities may have led some patients to refuse this option, with the aggravating factor that this could not always be performed in the first 14 days, as recommended.^{1,2}

Conclusion

We highlight, as a clear answer to our research question, that MetS is a risk factor for a worse outcome in terms of hearing recovery after ISSHL, regardless of age, gender, initial PTA and autoimmunity. We emphasize that all patients diagnosed with ISSHL should be actively inquired about elements that may underlie a possible case of MetS, since this can affect the prognosis of the patients.

Ethics Approval

The hospital's ethics committee approved the study (under protocol n. 111/2020).

Availability of Data and Material

The data and material pertaining to the present study can be made available upon reasonable request.

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Conflict of Interests

The authors have no conflict of interests to declare.

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